

Early origin of coronary heart disease (the "Barker hypothesis")

Hypotheses, no matter how intriguing, need rigorous attempts at refutation

See pp 423, 428, 432, 436

Risk profiles for coronary heart disease are surely among the most valuable products of epidemiology of the past half century. Not only have some important personal determinants of coronary heart disease been uncovered but also methods for their amelioration have been developed, and best of all, in many countries rates of cardiac disease have fallen steadily for 25 years.

Yet for some time now quietude has beset this field of research. The main risk factors—raised body weight, cholesterol concentration, and blood pressure; glucose intolerance; smoking; and lack of physical activity—are old discoveries, and much current research seems merely to be fine tuning these standbys. The precise role of variations in coagulation profiles in the pathogenesis of coronary heart disease remains hazy, and factors such as stress and social support seem no more and no less promising and ambiguous than they were decades ago.

So the excited welcome given to a totally new set of antecedents is unsurprising. The hypothesis of Professor David Barker and colleagues working in Southampton is that "a baby's nourishment before birth and during infancy," as manifest in patterns of fetal and infant growth, "programmes" the development of risk factors such as raised blood pressure, fibrinogen concentration, and factor VIII concentration and glucose intolerance and hence these are key determinants of coronary heart disease.

Since 1987 the group has elaborated this hypothesis in at least 40 papers (many of them in the *BMJ*) and two books.^{1,2} Although some evidence comes from comparisons among populations, the most recent approach has been to seek places where infant anthropometric measures were systematically recorded many years ago (Hertfordshire and Preston). Middle aged and elderly survivors have then been searched out for study. This idea is in line with a body of research of the past 50 years on the deferred effects of fetal exposure to viral infections, the atomic bomb, undernutrition and famine, hormonal treatment in pregnancy, and smoking.

None of the Southampton studies provides an actual measure of nutritional intake in mothers or babies. Early nutrition is inferred indirectly from fetal and infant growth, and fetal growth especially is a doubtful surrogate measure. Thus even if we take the findings as valid we still must ask whether nutrition or some other effect is being measured. In addition, inconsistencies in the data, with many findings failing to support the "baby's nourishment" hypothesis, have not gone unnoticed,³ and evidence contrary to the early experience hypothesis has been published.⁴

This week's journal contains four relevant studies. One paper is a further contribution from the Hertfordshire cohort⁵ (another paper from this cohort was published last month⁶), whereas the three other papers cast doubt on some aspects of the early nutrition thesis.

Strachan *et al* find mixed evidence about whether the health of migrants in England relates to where they came from or where they went to.⁷ Although for coronary heart disease, initial and current place of residence contribute equally to the risk of death, for stroke, current place of residence contributes more, particularly if it is London. This kind of analysis, limited to place of origin (which is not necessarily place of birth) rather than to individual exposures in early life, strongly suggests the potential for confounding by migration in the Southampton studies but does not constitute a direct test of the hypothesis.

Inconsistent support

The two papers from Southampton support the hypothesis inconsistently. Although in men weight at age 1 predicts cardiovascular disease in their 60s, birth weight does not.⁸ On the other hand, it seems at first glance that in women of the same age birth weight, but not infant weight, is significantly associated with some risk factors for coronary heart disease (low/high density lipoprotein cholesterol concentration and most measures of glucose intolerance), although not with others (blood pressure and concentrations of total cholesterol, fibrinogen, and factor VIII).⁹

The significant associations with birth weight are suspect because they are controlled for current body mass index; from inspection of the raw data we guess that without this adjustment many would not hold up. Body mass index may well be an intervening variable; to adjust for such a variable is to overcontrol and, usually, to misinterpret.

Body mass index is a much more powerful predictor of insulin concentrations than is birth weight (see tables III and IV³) and is positively related to birth weight. So to control for current body mass index when assessing the effect of birth weight is to cancel out the positive effect of birth weight on body mass index and thence on risk of glucose intolerance. This allows the effect of birth weight in the direction favoured by the authors to remain unopposed. The baby's nourishment hypothesis is not easily reconciled with the finding in this paper that plasma insulin concentration relates to current body mass index much more strongly than to birth weight.

A paradox inherent in the scientific method is that, attached though we are to the hypotheses we formulate, we must subject them to assault and search for circumstances that really test their resilience. Hypotheses, as Silverman has written, citing Galileo, must be "subjected to an ordeal."⁸ The results of the ordeal may prove consistent with the hypothesis or inconsistent with it, forcing its reformulation. When a hypothesis is clearly focused reformulation is possible; when it is broad and fuzzy no reformulation is necessary as much of the evidence can be incorporated into it. Thus the inconsistency in the results from Southampton is linked to the failure to specify hypotheses more tightly focused than "a baby's nourishment . . . influences the diseases it will experience in later life."⁹

With so broad a hypothesis, researchers are free to test the relation between a whole range of possible markers of a baby's nourishment and any diseases it will experience and to pronounce important those relations that are confirmed. In this work, researchers faced with findings that fail to support the hypothesis seem not to be treating them as threats to the integrity of the hypothesis.

The notion of induction, that knowledge is gained by the summarising of facts and experiences, has fallen on hard times as a credible approach to research. Indeed, it is easy to see the barrage of papers from Barker's group as an inductionist's delight. Example is piled on example, each somewhat consistent with the hypothesis but none seriously testing it. Francis Bacon, the founding father of the inductionist approach, advocated something else: "The induction which is to be available for the discovery and demonstration of sciences and arts must analyse nature by proper rejections and exclusions, and then after a sufficient number of negatives, come to a conclusion on the affirmative instances."¹⁰ What is missing in this work so far is the rigorous testing by rejections and exclusions—that is, by deliberate attempts at refutation.¹¹

Some ordeals

Two papers in this issue suggest some ordeals to which the baby's nourishment hypothesis might be subjected, and we add some more:

- Twins have greatly restricted fetal growth in the third trimester. But Christensen *et al* report that the mortality among surviving twins differs little from that among the general population.¹² Given that cardiovascular disease is the leading cause of death in older adults, an effect of growth retardation would be expected. The Southampton group has not provided any information about twins.

- One of the strongest associations uncovered by the Southampton group is the relation between a high ratio of placental weight to birth weight and subsequent risk factors for coronary heart disease.¹³ But what exactly influences placental weight? The Southampton group suggests anaemia (thus bringing in nutrition). But maternal diabetes,¹⁴ maternal smoking,¹⁵ and gestational age¹⁶ may influence the relation of birth weight to placental weight. And now Perry and colleagues in this issue raise the possibility that maternal obesity may as well.¹⁷ No account has yet been taken of these variables by the Southampton group.

- Much of the support for the early nutrition hypothesis comes from observations of subjects who constitute a very small proportion of the birth cohort from which they arose. Selection bias is likely to be operating. Attrition by death, migration, and simple "untraceability" is virtually never distributed equally across groups at risk. What would the results look like if access were available to a cohort in whom the losses were not so extreme?

- Smoking by the mother is a key determinant of both birth weight and smoking in offspring and hence of coronary heart disease in them. What would the results look like if smoking in the mother was an additional factor in the equation?

- Social class exerts its noxious effects on health in many ways. Would the findings still hold if we truly knew the social status of the subjects throughout their lifetime, as well as that of their parents? In neither of the two most recent papers from Southampton did the measure of social class at birth—occupation of the father—correlate with either birth weight or weight at age 1 in England in the 1920s. The absence of these highly consistent and well recognised associations points to weak measures and misclassification of either the social background or the growth of the child, or both, if not to biased sampling of the population.

- Most importantly, infant anthropometry is taken as a proxy for fetal and infant nutrition, although many other factors can affect these measures. What would the results look like if the exposure were nutritional intake itself? The best available evidence indicates, firstly, that only below a famine threshold does nutritional deprivation cause more than minor retardation of fetal growth and, secondly, that only in the third trimester are the effects substantial.

Now test it

The Southampton group has provided an intriguing but very general hypothesis, often ingeniously pursued, that has served to provoke the somewhat complacent world of cardiac epidemiology. As a hypothesis with substantial implications for public policy it deserves rigorous testing. This must include a much more careful and specific a priori formulation of the component parts of the baby's nourishment hypothesis and, especially, a careful search for (and willingness to take advantage of) opportunities to subject the resultant hypotheses to true ordeals.

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